Group2
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Mammalian Germ Cells Are Determined After PGC Colonization Of The Nascent Gonad

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In this article, as timing and location how mammalian primordial germ cells (PGCs) irreversibly commit to gametogenesis are investigated. Undestanding the transcriptional alterations that occur upon PGCs movement from uncommitted precursor to fully committed germ cells after colonizing the gonads is aimed. Role of RNA-binding protein DAZL in limiting PGCs'developmental potential and how it pushes them to commitment to gametogenesis is investigated in this study as DAZL is considered as a crucial part of this process. Furthermore, molecular mechanisms and evolutionary conservation across mammal and other animals have been taken into consideration due to its importance in germline specialization timing. Moreover, how errors in this process may give rise to human germ cells, such as testicular teratomas is examined which enables insight for both normal development and disease.

The researchers used RNA sequencing to analyze gene expression during PGC colonization and discovered multiple elevated genes, including DAZL, SLC25A31, SMC1B, DDX4, TDRD12, and MAEL, implying that the colonization program in mice is conserved in humans. They reduced 74 potential genes to ten gonad-specific genes expressed mostly in germ cells of embryonic gonads. Using Nanog-GFP and Dazl-tdTomato reporters, they discovered that Dazl-deficient cells expressed Nanog more, which was validated by flow cytometry. They next employed FACS to generate an EG cell line (Fig. 1 & 2). They related Dazl deficiency to increased teratoma formation, as seen by heterozygous host and teratoma genomes, implying that teratomas formed from mitotic germline cells rather than meiotic reactivation (Fig. 3). The testis was shown to be more favorable than the ovary for teratoma formation, as seen by gonadal sex reversal using Sry transgenes, and apoptosis was connected to teratoma production via Bax-heterozygous lines (Fig. 4). Cross-species validation in pigs using TALEN-mediated gene editing revealed teratoma formation in DAZL-deficient females and PGC differentiation failure in males, as evidenced by Sertoli cells and SOX9 protein (Fig. 5). Finally, conditional knockout tests demonstrated that a brief embryonic Dazl expression is sufficient for germline survival and female oogenesis but is required for male postnatal spermatogenesis (Fig. 6).

Using reporter systems, the study examined the relationship between Dazl expression and Nanog, one of the important Yamanaka factors. Although this method brought their interdependency to light, the investigation was constrained by focusing exclusively on Nanog. It could have been easier to see how pluripotency turns into differentiation if other pluripotency markers, such as Oct4, Sox2, and Klf4, had been included. In order to reduce strain-specific biases, the authors additionally examined the developmental potential of Dazl-deficient mice from four different genetic backgrounds. They did not, however, investigate how

particular genetic backgrounds might make up for Dazl's passing. These compensatory strategies may be clarified by looking at the genes involved in germ cell differentiation and pluripotency maintenance. Additionally, they assessed whether transient DAZL expression was adequate for germline commitment, indicating that DAZL may not be required for subsequent gametogenesis phases. A follow-up study could explore if delayed activation could correct prior inadequacies by temporarily activating DAZL expression following gonadal migration using methods like Cre-loxP or CRISPRa. Lastly, the study connected the risk of teratoma formation to the sexual identity of the somatic gonad, which is regulated by the SRY region. It did not, however, investigate the potential effects of SRY-regulated pathways on tumor formation or germline differentiation, such as BMP or WNT signaling. Further research into these networks may shed light on the mechanisms in which somatic-germline interactions support tumor suppression and germline development.